N-(5-Fluoro-2-phenoxyphenyl)-*N*-(2-[^{18}F] fluoroethyl-5-methoxybenzyl)acetamide [^{18}F]FEDAA1106

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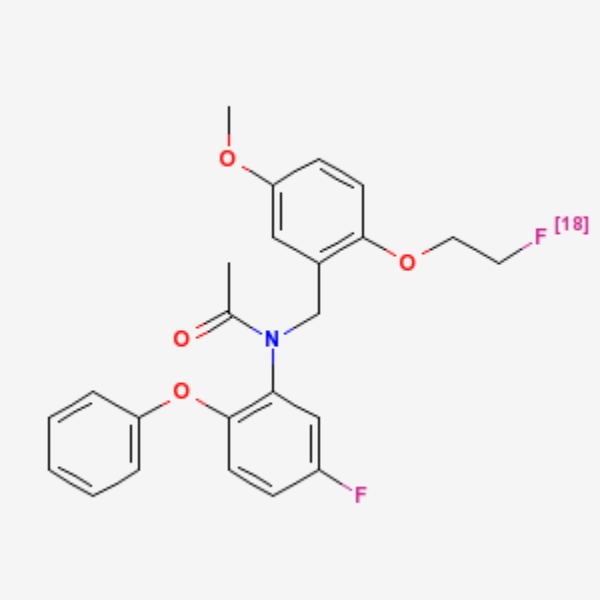
Chemical name: *N*-(5-Fluoro-2-phenoxyphenyl)-*N*-(2-[^{18}F]fluoroethyl-5-methoxybenzyl)acetamide
Abbreviated name:
Synonym: [^{18}F]FEDAA1106
Backbone: Compound
Target: Peripheral-type benzodiazepine receptor
Mechanism: Receptor binding
Method of detection: PET
Source of signal: ^{18}F
Activation: No
***In vitro* studies:** Yes
Rodent studies: Yes
Other non-primate mammal studies: No
Non-human primate studies: Yes
Human studies: Yes



Click on the above structure for additional information in PubChem [http://pubchem.ncbi.nlm.nih.gov].

Background

[PubMed]

Benzodiazepines, such as diazepam, are potent psychoactive drugs used for their sedative and anxiolytic properties (1, 2). There are two types of benzodiazepine receptors, which have been designated as the central and peripheral benzodiazepine receptors. The central benzodiazepine receptor (CBR) is found exclusively in the central nervous system on the membranes of neurons and is coupled to the γ-aminobutyric acid receptor/chloride channel (3). In contrast, the peripheral benzodiazepine receptor (PBR) is a mitochondrial protein found in brain and peripheral tissues (adrenal gland, heart, lung, kidney, and testis) (4). The brain has lower levels of PBRs than do the peripheral tissues. Both glial cells and macrophages contain high levels of PBRs (5-7). Increased

PBR expression after brain injury or neuroinflammation is associated with microglial activation, such as occurs with the neuronal damage accompanying several neurodegenerative diseases, including Alzheimer's disease, Wernicke's encephalopathy, multiple sclerosis, and epilepsy.

PBRs have been studied *in vivo* by positron emission tomography (PET) using [^{11}C]PK11195 [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=micad.chapter.PK11195-11C], an isoquinoline carboxamide with specific PBR-antagonistic activity. [^{11}C]PK11195 is being developed as a PET agent for non-invasive studies of microglia and macrophage activation in the brain, lung, and heart. However, accumulation of this tracer in the brain is limited. *N*-(2,5-Dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide (DAA1106) was found to be a selective agonist for studying PBRs in the central nervous system (8, 9). DAA1106 was reported to have a higher affinity for PBRs in mitochondrial fractions of rat and monkey brains than did PK11195 (8, 9). Therefore, both tracers are able to cross the normal cell membrane to reach the mitochondrial receptor sites. [^{11}C]DAA1106 [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=micad.chapter.FEDAA1106-18F] has been studied as a PET agent for the non-invasive study of microglia and macrophage activation in the brain. [^{11}C]DAA1106 binding was 3-fold higher than [^{11}C]PK11195 binding in the monkey occipital cortex (9). *N*-(5-Fluoro-2-phenoxyphenyl)-*N*-(2-[^{18}F]fluoroethyl-5-methoxybenzyl)acetamide ([^{18}F]FEDAA1106), a fluoroethyl analog of DA1106, is being developed as a potential PET ligand with highly selective and specific binding to PBR.

Synthesis

[PubMed]

In the report by Zhang et al. (10), [^{18}F]FEDAA1106 was synthesized by alkylation of *N*-(5-fluoro-2-phenoxyphenyl)-*N*-(2-hydroxy-5-methoxybenzyl)-acetamide with 2-[^{18}F]fluoroethyl bromide ([^{18}F]FCH_2CH_2Br) in the presence of NaH. [^{18}F]FCH_2CH_2Br was prepared by the reaction of [^{18}F]F^- with 2-bromoethyl triflate ($BrCH_2CH_2OTf$), using an automated system. Subsequent high-performance liquid chromatography (HPLC) separation gave a radiochemical purity >98%. The specific activity was 120 GBq/μmol (3.2 Ci/μmol) at end of synthesis with 12 ± 4% radiochemical yield. Total synthesis time was 50 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro [^{11}C]DAA1106 PBR-binding studies showed IC_{50} values of 0.77, 1.62 and 8.26 nM for FEDAA1106, DAA1106, and PK11195, respectively (10). All three compounds had little affinity for CBRs as measured by [^{11}C]flumazenil binding assays. Hence, FEDAA1106 is 10-fold more potent than PK11195. *In vitro* binding studies of [^{3}H]DAA1106 produced K_d values of 0.12 ± 0.03 and 0.43 ± 0.04 nM for mitochondrial fractions of rat and monkey cerebral cortex, respectively (9). The PBR B_{max} values were 161.03 ± 5.8, and 701 ± 70 fmol/mg protein for mitochondrial fractions of rat and monkey cerebral cortex, respectively. Regional distribution of [^{3}H]DAA1106 in mitochondrial fractions of the rat brain revealed that the olfactory bulb has the highest B_{max} (>400 fmol/mg protein),

followed by the cerebellum, cerebral cortex, hypothalamus, striatum, hippocampus, and thalamus. This pattern of DAA1106 binding in the brain was later confirmed by *in vitro* autoradiographic studies using [^{11}C]DAA1106 in rats.

Animal Studies

Rodents

[PubMed]

Zhang et al. (10) reported *ex vivo* autoradiographic accumulation of [^{18}F]FEDAA1106 in all brain regions at 30 min after injection. The highest uptake was in the olfactory bulb (0.8 fmol/mm^2), followed by the cerebellum (0.37 fmol/mm^2) and cerebral cortex (0.2 fmol/mm^2). Coadiministration of unlabeled DAA1106 decreased the accumulation in all brain regions with the most significant reduction in the olfactory bulb (80% inhibition) followed by the other regions (40-60% inhibition). Almost all of the radioactivity in the brain was intact [^{18}F]FEDAA1106 at 30 min after injection. Because the target receptor is in the mitochondria, the compound has to cross the blood-brain barrier and the cell membrane readily to reach its target. About 29% of radioactivity in the plasma was intact [^{18}F]FEDAA1106 at 30 min after injection.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

Zhang et al. (11) reported PET studies of [^{18}F]FEDAA1106, [^{11}C]DAA1106, and [^{11}C]*R*-PK11195 in monkey brain. [^{18}F]FEDAA1106 displayed high uptake in the occipital cortex, a region rich in PBRs. The radioactivity level of [^{18}F]FEDAA1106 in monkey brain was 1.5 times higher than that of [^{11}C]DAA1106 and 6 times higher than that of [^{11}C]*R*-PK11195. The accumulation of [^{18}F]FEDAA1106 was inhibited significantly by pretreatment of PK11195 (5 mg/kg) or DAA1106 (1 mg/kg), indicating that the binding of [^{18}F]FEDAA1106 in the monkey brain was mainly attributable to PBRs. Metabolite analysis in the plasma revealed that [^{18}F]FEDAA1106 was metabolized by debenzylation to a polar product, which was not detected in the mouse brain. About 50% of radioactivity in the plasma was intact [^{18}F]FEDAA1106 at 30 min after injection.

Human Studies

[PubMed]

Fujimura et al. (12) reported PET studies with [^{18}F]FEDAA1106 in 7 healthy men. Regional distribution in the brain was assessed by binding potential (BP), which was calculated by nonlinear least-squares (NLS) analysis based on the two-tissue compartment model, and distribution volume

(DV), which was estimated by NLS, Logan plot, and multilinear analysis methods. The DVs estimated with each of the methods were significantly correlated. There was also significant correlation of BP with NLS and DV with NLS, Logan plot, or multilinear analysis. The simulation studies indicated that NLS is a suitable method for the estimation of [^{18}F]FEDAA1106 binding to PBRs. Internal dosimetry data for [^{18}F] FEDAA1106 in humans are not available in the literature.

References

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